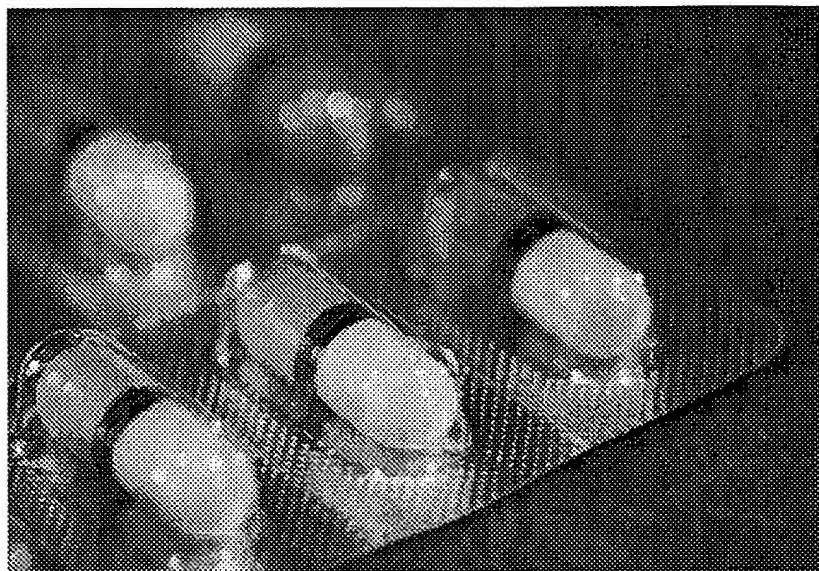


Pharmaceutical Blister Packaging, Part I

Rationale and Materials

Ron Pilchik

Eighty-five percent of solid drugs in Europe are packed in blisters, compared with less than 20% of those in the United States. However, blister packaging is becoming more accepted in the United States as both manufacturers and consumers recognize its benefits. This article discusses the materials used for blister packages and typical blister constructions.



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Packaging is one of the largest industry sectors in the world, worth \$280 billion. Consumer healthcare packaging represents 4% (\$11.2 billion) of the packaging industry. As drug manufacturers approach the 21st century, they face a number of challenges that packaging can help them meet.

A decade ago packaging often was an afterthought for many pharmaceutical companies, viewed as merely the final step in manufacturing. But now firms must consider packaging earlier during the development process. Pharmaceutical packaging is quickly becoming an essential part of the drug delivery system as well as a core element of the marketing mix, through which manufacturers can differentiate their products from those of their competitors. The demand for pharmaceutical packaging is increasing and will continue to increase as companies rely more on packaging and labeling as

media to protect and promote their products, increase patient compliance, and meet new regulations.

Basic configuration of blister packaging

Background. Two basic types of pharmaceutical blister packages exist. In one variety the cavity is constructed of clear, thermoformed plastic, and the lid is formed of clear plastic or a combination of plastic, paper, and/or foil. The other type of package contains foil as an essential component of both webs, and its cavity is created by cold stretching. Figure 1 shows the basic configuration of a blister pack.

In the early 1960s, Karl Klein designed the first machinery for producing push-through blister packaging. He did not obtain a patent for the design because the European pharmaceutical industry was not very interested in it — that is, until

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the birth control pill was formulated a few years later. For this revolutionary product Schering (Berlin, Germany) chose blister packaging because it seemed to be the most appropriate way to package the pill for effective administration.

Thus the most important reason for introducing blister packaging technology was to offer patients a clearly marked individual dose, enabling them to check whether they had taken the prescribed drugs on a given day. Moreover, the drugs that were not taken remained in the original package and were fully protected against adverse external conditions. The patient could handle the blister package more easily and could store it more conveniently than conventional packages.

Very soon, manufacturers and packagers recognized other advantages of blister packaging such as the prevention of broken glass bottles and reduced costs and higher packaging speeds relative to other packaging materials. Another important benefit became apparent later: It is easier to prove misuse with blister packaging than with conventional packaging. Thus, blister packages effectively meet the demand for tamper-evident packaging. All these advantages explain why blister packaging is used for approximately 85% of solid drugs in Europe.

Use in Europe versus use in the United States. The situation is just the opposite in the United States, where virtually all over-the-counter and prescription drugs are packaged in bottles. For example, less than 20% of nonliquid pharmaceutical products in the United States currently are sold in blister packs.

There has been a great deal of speculation about the causes for the difference in the use of blister packaging in the United States and Europe. First, following World War II, European packaging machinery (like almost everything else) lay in ruins. Drug packagers in Europe started over from scratch, and when they did they chose blister machinery over bottle equipment. Second, European regulations on child-resistant closures are far less stringent than rules in the United States.

A third reason lies in the differences among health plans in the two areas. In Europe, most health plans limit the number of units that can be prescribed at one time to a 10- to 14-day supply. In the

United States, however, insurers allow a longer supply period, typically 30 to 60 days. The smaller European purchase quantity favors blister packaging because it costs less to package small numbers of items in blisters than in bottles. Finally, the European community has stronger environmental incentives to use blister packaging. For example, manufacturers are penalized for introducing excessive material into the system. The use of blister packaging allows manufacturers to reduce packages to a minimal size.

Increased use in the United States. Blister packaging is becoming more accepted in the United States as pharmaceutical manufacturers and consumers recognize its benefits. Blister packs can help patients follow drug regimens, protect drugs over a long shelf life, and are portable. Advocates of blister packaging in the United States cite five aspects in which blister packaging is better than conventional packaging.

- product integrity
- product protection
- tamper evidence
- reduced possibility of accidental misuse
- patient compliance.

Product integrity. The retail-level preparation of prescription drugs in the United States is troubling. Pharmacists or pharmaceutical technicians count pills in the uncontrolled atmosphere of the supermarket and drug store, where many factors can negatively affect sensitive drugs as they are transferred from container to container.

Blister packaging helps retain product integrity because drugs that are prepackaged in blisters are shielded from adverse conditions. Furthermore, opportunities for product contamination are minimal, and each dose is identified by product name, lot number, and expiration date. Therefore, blister packaging ensures product integrity from the producer directly through distribution to the consumer.

Product protection. Blister packaging protects pharmaceuticals in the home better than bottles do. For example, most consumers store their medicines within the medicine cabinet in the bathroom. But the bathroom environment periodically is filled with clouds of steam. As a result, it may be no exaggeration to say that once

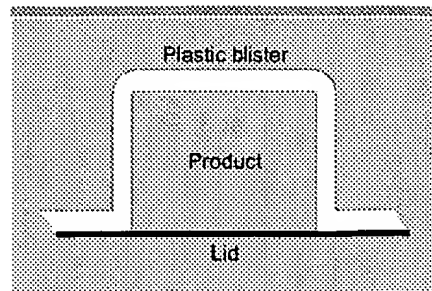


Figure 1: The basic configuration of blister packaging.

an opened bottle of pills has been stored under these conditions, the unused pills will never be the same.

Blister packaging, however, keeps each tablet or capsule hermetically sealed in its own bubble. Drugs that are not taken remain in the original package and are fully protected against external conditions. A blister protects a moisture-sensitive tablet right up to administration. In contrast, the moisture in the headspace of a multiple-unit bottle is replaced each time the bottle is opened.

Tamper evidence. Tamper evidence is another strength of blister packaging. The dosage units are individually sealed in constructions of plastic, foil, and/or paper. The package must be designed so that one must tear the compartment to get at the product, and it must not be possible to separate the backing materials from the blister without leaving evidence. Once a bottle has been opened, whatever tamper-evident mechanism it had is gone. With blister packaging, however, each tablet or capsule is individually protected from tampering until use, so any form of tampering with a blister package is immediately visible.

Possibility of accidental misuse. Blister packaging also can be made child resistant, and several such designs currently are in use. Most child-resistant blister packages contain a paper/film layer with a peelable adhesive. Patients must peel the adhesive away from the foil backing before the pill can be pushed through. Specifying 15-mil polyvinyl chloride (PVC) blister stock provides extra security because it is less likely that children could puncture the package by biting through it. Companies also are experimenting with bitter coatings to deter children from putting packages in their mouths.

Patient compliance. Finally, an additional

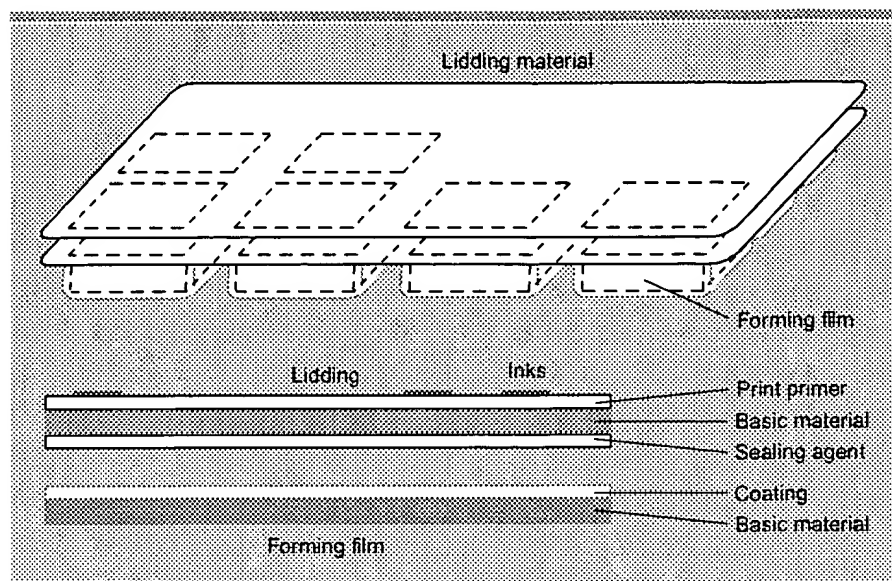


Figure 2: Basic components of blister packaging.

Table 1: Comparison of forming films.

Type and Thickness of Forming Film (mil)	WVTR (g/m ² /day)*	Price per Unit Area**
PVC (10)	1.1	1
PVC/PVDC (10/1.2)	0.17	2.1
PVC/CTFE (8/0.76)	0.07	2.1
PP (12)	0.20	1.3
PET (10)	2.6	1.4
PS (12)	6	1.2
OPA/aluminum/PVC (1/1.8/2.4)	0	2.9

*As measured on the unformed film at an ambient temperature of 20 °C and 65% RH.

**Where 1 represents the price per unit area of 10-mil PVC.

benefit is the role of blister packaging in compliance. As many as 30% of all prescriptions are not taken properly initially, and as many as 50% are not continued after one year. Such misuse can cause a range of adverse drug reactions, including death.

The Healthcare Compliance Packaging Council (HCPC, Washington, DC) was formed in 1990 as a nonprofit corporation to educate consumers, professionals, and policymakers in the healthcare field about the role of blister packaging in pharmaceutical compliance. Following are some of the relevant data that HCPC has uncovered in recent studies in the United States:

- A total of 1.8 billion prescriptions are given each year, and half are taken incorrectly.
- Ten percent of all hospital admissions result from pharmaceutical noncompliance.

- The cost of such noncompliance is estimated at \$13–15 billion annually.
- Twenty-three percent of the people admitted to nursing homes are aged and cannot manage their medications in their own homes.
- An estimated 125,000 people in the United States die each year because they do not take medications as prescribed.
- The elderly population, which consumes roughly 50% of all prescription drugs, is growing, making abuse problems even more critical.

Furthermore, blister packs can be bar coded for use in hospitals and nursing homes to prevent errors in distributing medication. One final important benefit of blister packaging in patient compliance is that pharmacists have a greater opportunity to communicate with and advise their patients because less time is necessary to fill the prescription.

The use of blister packaging in the United States is on the rise. For example, several years ago the states of New York and New Jersey adopted regulations requiring hospitals to implement unit-dose blister-packaging distribution systems. The New Jersey Society of Hospital Pharmacists cited reports showing that fewer medication errors occur in such unit-dose blister package systems. Logic would seem to dictate that more states will adopt similar regulations.

Blister packaging components

The four basic components of pharmaceutical blister packages are the forming film, the lidding material, the heat-seal coating, and the printing ink (see Figure 2). The most common blister package in the United States is made of a foil, film, paper, or multimaterial backing that is adhered to a sheet of thermoformed plastic bubbles. Forming films account for approximately 80–85% of the blister package, and lidding materials make up 15–20% of the total weight of the package. Because the forming film and the lidding material form an integrated package, they must match precisely.

Forming film

The forming film is the packaging component that receives the product in deep-drawn pockets. One key to package success is selecting the right plastic film for the blisters in terms of its property type, grade, and thickness. Consideration must be given to the height and weight of the product, sharp or pointed edges of the final package, and the impact resistance, aging, migration, and cost of the film. The plastic also must be compatible with the product. Factors influencing package production and speed of assembly must be taken into account, including heat-sealing properties and the ease of cutting and trimming formed blisters.

Characteristics. Plastic forming films such as PVC, polypropylene (PP), and polyester (PET) can be thermoformed, but support materials containing aluminum are cold-formed. The forming film usually is colorless and transparent, but it can be obscured for use in child-resistant packages or to protect light-sensitive drugs. The forming web for blister packs nearly always is PVC, sometimes

coated or laminated with additional components that enhance the oxygen and water-vapor barrier. Table I compares the water-vapor transmission rate (WVTR) and the price per unit area of various forming films.

Types of forming films. PVC forming film is called *rigid PVC* because it is almost free of softening agents. Rigid PVC is a very clear, stiff material with a low WVTR. It exhibits excellent thermoformability; a high flexural strength; good chemical resistance; low permeability to oils, fats, and flavoring ingredients; easy tintability; and low cost. These properties make rigid PVC the material of choice for blister packaging, and it essentially has 100% of the market for the plastic component. PVC films that are thermoformed have a thickness of about 10 mil.

The use of PVC has attracted much criticism because its combustion produces hydrochloride emissions and, under unfavorable conditions, highly toxic dioxins. Legislation in Germany and Switzerland prohibits the incineration of PVC, the principal method of disposal used in those countries. This has created a bias toward the use of PP for blister packaging in Europe, where many pharmaceutical companies now stipulate that any new blister machines must be capable of handling both PVC and PP.

Polyvinylidene chloride (PVDC)-coated PVC. Although its volume in drug packaging is small, PVDC plays a critical role in blister packaging as laminations or coatings on PVC. PVDC is the most common coating in blister packaging because it can reduce the gas and moisture permeability of PVC blister packages by a factor of 5–10. Coated PVC films have a thickness of 8–10 mil; the thickness of the PVDC coat amounts to 1–2 mil. The coating is applied on one side and usually faces the product and the lidding material.

PVC/chlorotrifluoroethylene (CTFE). Films made from PVC and CTFE have the lowest water-vapor permeability of all films used for blister packaging. When compared with the water-vapor permeability of 10-mil PVC, the permeability of 8-mil PVC/0.76-mil CTFE is lower by a factor of 15. However, the environmental concerns regarding PVC also apply to PVC/CTFE films.

PP. There is an increasing trend toward using PP as a support material for blister

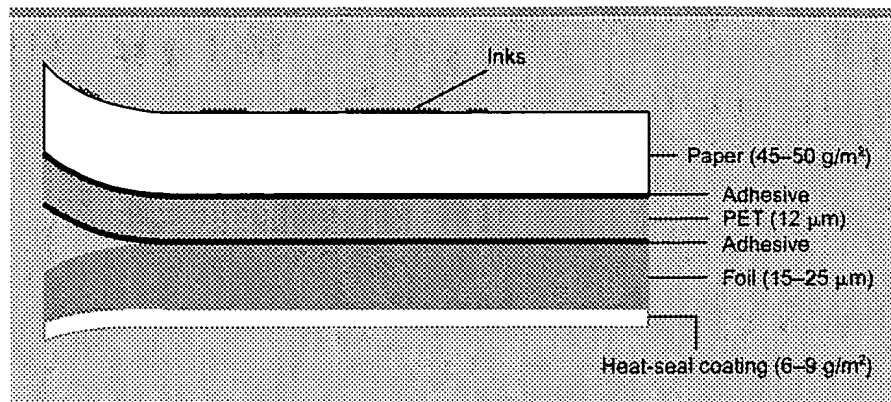


Figure 3: Cross section of a peel off-push through lidding material.

packages. The water-vapor permeability of uncoated PP is lower than that of PVC and is comparable to that of PVDC-coated PVC. The thickness of PP films used in the thermoforming process ranges from 10 to 12 mil.

Advantages of PP include easy recyclability, no release of toxins during incineration, and good moisture-barrier properties. PP is a possible replacement for PVC, especially in Europe.

However, the use of PP has its drawbacks. One problem is thermoforming. The temperatures required for thermoforming PP and for the subsequent cooling process must be controlled precisely. Warping also can occur, in which case the packages must be straightened before cartoning. Other difficulties associated with the use of PP include its thermal instability, higher rigidity than PVC, and susceptibility to postprocessing shrinkage.

In addition, PP is difficult to run on a standard blister machine and cannot be processed as fast as PVC. If a company runs PP and needs new equipment, it must go through a precise validation process, performing various tests on PP to satisfy FDA requirements. As a result, PP is virtually nonexistent in pharmaceutical blister packaging in the United States, and it still appears to be used minimally for that purpose in Europe.

PET is another material that may replace PVC, but its relatively high water-vapor permeability compared with that of PVC will prevent its universal use. PVDC-coated PET could have the same water-vapor barrier effect as PVC, but this does not appear to be promising in view of the larger goal to replace chlorous plastics with PET.

Polystyrene (PS) is perfectly compatible with thermoforming, but its high water-vapor permeability makes it unsuitable as a blister material for pharmaceutical purposes.

Oriented polyamide (OPA)/aluminum/PVC or nylon/aluminum/PVC. OPA/aluminum/PVC laminates are intriguing. With a laminate structure consisting of 1-mil OPA, 1.8-mil aluminum, and 2.4-mil PVC it is possible to eliminate water-vapor permeability almost entirely. Moreover, because of the large proportion of aluminum in the laminate, recycling this material has become feasible (particularly because most lidding materials also contain aluminum). Enormous efforts are being made to replace PVC with PP in such laminates to comply with environmental standards.

Like other laminates containing aluminum, the OPA/aluminum/PVC laminate is cold-formed. Its cost per square meter can stand any critical comparison with PVDC-coated PVC. Cold-forming, however, requires more packaging material than does thermoforming to package the same number of the same size of tablets or capsules.

CTFE homopolymer. Honeywell (Morristown, NJ) recently introduced a 3-mil CTFE homopolymer barrier film (Aclar UltRx 3000) that can be thermoformed easily and that exhibits the highest moisture barrier of clear films. This reflects the trend toward the use of higher-barrier materials. Various Aclar products have allowed wider use of blister packaging because they can be thermoformed into clear or tinted blister cavities and exhibit barrier properties close to those of the near-perfect barrier offered by foil.

Table II: Comparison of lidding materials.

Lidding Material	Price per Unit Area (p/m ²)	Weight*
0.8-mil Aluminum, hard, push-through	60	1
0.8-mil Aluminum, hard, heat seal-coated, side-printed, push-through	61	1.25
1-mil Aluminum, soft, child resistant	76	1.15
45 g(m ⁻²)/1-mil Paper/aluminum, peel-off	121	1.55
45 g(m ⁻²)/0.48-mil Paper/PET/aluminum, peel off-push through	142	2.00

*Where 1 represents the price per unit area of 0.8-mil, hard, push-through aluminum.

Lidding materials

The lidding material provides the base or main structural component upon which the final blister package is built. It must be selected according to the size, shape, and weight of the product as well as the style of the package to be produced. Lidding materials range in caliper or thickness from 0.36 to 0.76 mm, but 0.46–0.61 mm is the most popular range. The surface of the lidding material must be compatible with the heat-seal coating process. Clay coatings are added to the lidding material to enhance printing. Heat-sealing and printability are both important considerations in blister packaging, and the lidding material must offer the best workable compromise.

Characteristics. The lidding material can be clear plastic, but in pharmaceutical packaging it is either plain or printed 1-mil foil (for push-through blister types) or paper/foil or paper/PET/foil laminations (for child-resistant peel-push types). The lidding material must guarantee a WVTR that is at least as low as that of the forming films, and it must be suitable for the type of opening appropriate to the package (e.g., push-through or peel-off). Figure 3 shows a cross-section of a peel off-push through lidding material. Table II shows the comparative cost per unit area of various lidding materials.

Types of lidding materials. Hard aluminum is the most widely used push-through lidding material in Europe. The foil usually has a thickness of 0.8 mil. There are endeavors, however, to reduce the thickness of this foil to 0.6 mil. The hardness of the aluminum facilitates push-through opening.

Usually, only the print primer side features a printed design, but occasionally the side with the heat-sealing coating also can

be printed. A double coat of heat-sealing coating (a heat-sealing primer and the actual heat-sealing coating) has become the standard for lidding materials.

The heat-sealing primer ensures optimum adhesion of the heat-sealing coating to the aluminum foil. The heat-sealing coating can then be matched to the formed films. If the heat-sealing primers are colored, applying the heat-sealing coating over the primer can protect the packaged product from coming in contact with the pigments. If additional printing is required on the side of the heat-sealing coating, the only alternative is to apply two coats of the coating. This technique is necessary because the printing inks must be located between the heat-sealing primer and the actual heat-sealing coating.

Soft aluminum (1 mil) frequently is used for child-resistant push-through foils. With the exception of the type of aluminum used, the structure of this lidding material corresponds to that of hard aluminum (0.8 mil). The softness and thickness of this type of aluminum help prevent children from pushing tablets through it. This material also is supplied with a perforation along the sealed seams so that it cannot be peeled off the formed film in one piece.

Paper/aluminum. In combinations of paper and aluminum, the weight of the paper amounts to 40–50 g/m². In Europe, the thickness of the aluminum typically is 0.28–0.48 pm, but in the United States it has a thickness of 0.6–1 mil. The reason for this difference lies in the fact that this lidding material is used in Europe for child-resistant push-through packages, so the aluminum foil must be relatively thin. In the United States, this type of material is used as a peel-off foil, so the foil must

be relatively thick for effective peeling. Because printing is applied to the side with the paper, no print primer is required. Virtually all of the previous comments regarding heat-sealing coating apply to combinations of paper and aluminum.

Paper/PET/aluminum. Lidding material made of a paper/PET/aluminum laminate is often called peel off-push through foil. This kind of material is used predominantly in the United States. The concept is to first peel off the paper/PET laminate from the aluminum and then to push the tablet through the aluminum.

Heat-seal coatings

For blister packages, heat-seal coatings are perhaps the most critical component in the entire system. The appearance and physical integrity of the package depends upon the quality of the heat-seal coating.

Heat-seal coatings provide a bond between the plastic blister and the printed lidding material. These solvent- or water-based coatings can be applied to rolls or sheets of printed paperboard using roll coaters, gravure or flexographic methods, knives, silk-screening, or sprays. Whatever the system, it is essential that the proper coating weight be applied to the lidding material for optimum heat-sealing results.

Characteristics. A successful heat-seal coating for blister packages must exhibit good gloss, clarity, abrasion resistance, and hot tack and must seal to various blister films. Hot tack is particularly important because the product usually is loaded into the blister and the lidding material heat-sealed in place (face down) onto the blister. When the package is ejected from the heat-seal jig, the still-warm bond line must support its entire weight. A relatively low heat-seal temperature is desirable for rapid sealing and to prevent heat distortion of the blister film.

Although heat-seal coatings used for blister packaging still are predominantly solvent-based vinyls (because of their superior gloss), water-based products are making some inroads. However, they must be evaluated carefully for hot-tack properties, gloss retention, adhesion to specific inks, and sealability to selected blister films.

In addition, the heat-seal coating must precisely match the lidding material and the plastic material of the forming films. *Precisely match* means that with pre-

determined sealing parameters, a permanent sealing effect between the lidding material and the forming film must be guaranteed under any climatic conditions. The heat-seal coating must also ensure constant sealing for any given sealing parameter. With the proper heat-seal coating, strong fiber-tearing bonds can be obtained. Specifically, the sealing strength must fall within predetermined tolerance limits and must be suitable for push-through or peel-off opening. The heat-seal coating also protects the printed area and provides a glossy finish. Most importantly, the heat-seal coating must comply with FDA recommendations.

Printing inks

Printing inks provide graphics and aesthetic appeal. They can be applied to the lidding material by letterpress, gravure, offset, flexographic, or silk-screen printing processes. Printing inks must resist heat-sealing temperatures as high as 300 °C without showing any discoloration or tackiness (blocking). In addition, they must sufficiently resist abrasion, bending, and fading and must be safe for use with the intended product. Printing inks should not contain excessive amounts of hydrocarbon lubricants, greases, oils, or release agents. Qualification tests should always precede production runs. Finally, printing inks must comply with FDA recommendations.

Cold-formed foil/foil

Best known to Americans is the blister package made of a foil, film, paper, or multimaterial backing that is adhered to a sheet of thermoformed plastic blisters.

However, a less common type of blister is the foil/foil lamination used for products that are particularly susceptible to moisture and/or light. Unlike all-plastic blisters, these are not thermoformed but instead are cold-pressed into shape.

Products that require the highest degree of protection are packed in an all-foil package. The use of cold-formable foils is growing because more moisture-sensitive drugs are on the market. Cold-formable foil is finding favor because it is the only material that provides a 100% barrier to moisture, oxygen, and light. This has helped expand the applications in which blisters can be used, allowing the blister packaging of sensitive products.

Characteristics. One element of the foil/foil blister pack comprises a lamination of plastic film (PVC or PE), adhesive, foil, adhesive, and an outer plastic film. The outer film, which can be PET or PVC, supports the thin aluminum layer and acts as the heat-seal layer. The aluminum layer usually consists of several very thin layers rather than a single thick one. The multiple layers help ensure that pinholes do not go all the way through the foil. They also increase the stretchability of the metal and facilitate the cold-stretching process.

Even so, the brittleness of cold-formed aluminum means that foil/foil blisters cannot be made as formfitting as plastic ones. These multilayer webs are formed, filled, and sealed on a machine that performs these functions in sequence much as the thermoform-fill-seal machine does except that neither web is heated before the forming step.

Process. During the cold-forming process, the foil is shaped and molded around a plug to form a cavity. As such, it is a marginally more expensive process than thermoforming, and its tooling is a bit more expensive than that of thermoformers. Upgrading is an option for many companies — most new machines can be converted to cold-form aluminum. One disadvantage is that the cavities must be made larger in the cold-forming process than during thermoforming, thus increasing the overall area of the package and often allowing the product to shift inside the blister.

Part II will discuss the technology of blister package processing and the future outlook for this packaging methodology.

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